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114. Abdul-Mohsen M. E. Omar*1 and Shun-ichi Yamada*2 : Studies on Thioamides. Ⅳ.*3 Extension of the Cyclodesulfurization Reaction to Synthesize 1-Substituted and 1,3-Disubstituted-3,4-dihydro-9*H*-pyrido[3,4-*b*]indole Derivatives.

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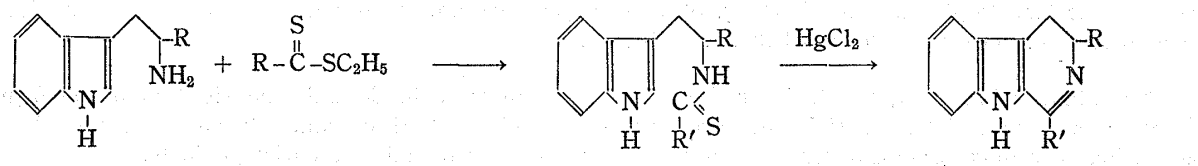
The previous report from this laboratory has declared the establishment of a new synthetic method of 1-substituted-6,7-dimethoxy-3,4-dihydroisoquinoline derivatives, independently from the classical Bischler-Napieralski reaction, through the cyclodesulfurization of N-(3,4-dimethoxyphenethyl)thioamides with mercuric chloride.[1]

In extension of the scope of this new type of ring closure to the synthesis of the 3,4-dihydro-9*H*-pyrido[3,4-*b*]indole nucleus, a series of three N-[2-(3-indolyl)ethyl]thioamides (Ⅱa~c) which are derived from tryptamine (Ⅰ : R=H) and N-(methylthiocarbonyl)tryptophan methyl ester (Ⅲ) were chosen to be cyclized to the corresponding 1-substituted and 1,3-disubstituted-3,4-dihydro-9*H*-pyrido[3,4-*b*]indole derivatives (Ⅳa~c and Ⅴa) as depicted in Chart 1.



Ⅰa : R=H
Ⅰb : R=$COOCH_3$

Ⅱa : R=H, R′=CH_3
Ⅱb : R=H, R′=C_6H_5
Ⅱc : R=H, R′=$C_6H_5CH_2$
Ⅲ : R=$COOCH_3$, R′=CH_3

Ⅳa : R=H, R′=CH_3
Ⅳb : R=H, R′=C_6H_5
Ⅳc : R=H, R′=$C_6H_5CH_2$
Ⅴa : R=$COOCH_3$, R′=CH_3
Ⅴb : R=COOH, R′=CH_3

Chart 1.

The required thioamides were conveniently prepared as demonstrated in Chart 1, by allowing a solution of either tryptamine (Ⅰ : R=H) or tryptophan methyl ester (Ⅰ : R=$COOCH_3$) in the minimum amount of methanol to react with dithioesters, according

Table I. Yield and Physical Properties of Some N-[2-(3-Indolyl)ethyl]thioamides (Ⅱa~c) and N-(Methylthiocarbonyl)tryptophan Methyl Ester (Ⅲ)

Compound No.	Yield (%)	m.p. (°C)	Recrystn. solvent	Mol. formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Ⅱa	86.6	126~127	benzene	$C_{12}H_{14}N_2S$	66.03	6.47	12.84	66.33	6.56	12.91
Ⅱb	93.1	117~119	benzene-hexane	$C_{17}H_{16}N_2S$	72.84	5.75	9.99	72.55	5.80	10.18
Ⅱc	83.7	129~130	benzene	$C_{18}H_{18}N_2S$	73.45	6.16	9.52	73.56	6.17	9.81
Ⅲ	90.0	102~104	benzene-hexane	$C_{14}H_{16}O_2N_2S$	60.86	5.84	10.10	61.06	5.91	10.21

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to the general procedure of preparing N-(2-arylethyl)thioamides,[2] and then recrystallizing the products from the proper solvents as specified in Table I.

On the other hand, our approach to effect cyclization of the thioamides (IIa~c) was made by applying the best conditions which produced the cyclized 3,4-dihydroisoquinoline derivatives in maximum yield.[1] Therefore, in all experiments, either three or four moles of mercuric chloride were used for each mole of thioamides. In acetonitrile, when such mixtures were stirred under reflux for seven hours, the reaction proceeded smoothly with the usual changes in the color of the reacting mixture from clear yellow to white turbid, yellowish brown with evolution of hydrogen chloride gas at the start of reflux and finally to deep brown with white creamy amorphous powder suspended in it. These observations showed that the sulfur atom of the starting materials was not abstracted directly as mercuric sulfide by mercuric chloride but removed as one of the component of the creamy amorphous powder as previously occurred in N-(3,4-dimethoxyphenethyl)thioamides.[1] The removal of mercuric chloride from the organic mercurials with hydrogen sulfide followed by treating the resultant to isolate the cyclized bases from the unreacted thioamides or the formed acid amides (see experimental part), afforded the required 1-substituted-3,4-dihydro-9*H*-pyrido[3,4-*b*]indole derivatives (IVa~c) in high yield ranging from 90 to 93% in case of using three moles of mercuric chloride and nearly the same with four moles of mercuric chloride as summarized in Table II.

Table II. Results of the Cyclodesulfurization of N-[2-(3-Indolyl)ethyl]thioamides (IIa~c) Using Different Moles of Mercuric Chloride

Compound No.	Moles of $HgCl_2$ per mole of thioamide	Solvent	Reflux period (hr.)	Yield of crude base (%)	m.p. of crude base (°C)
IIa	3	CH_3CN	7	93.6	178~180
〃	4	〃	7	82.9	178~180
〃	3	THF	7	39.5	176~177
〃	4	〃	7	53.4	175~177
IIb	3	CH_3CN	7	90.0	220~222
〃	4	〃	7	88.9	220~222
〃	3	THF	7	38.3	219~221
〃	4	〃	7	38.5	218~221
IIc	3	CH_3CN	7	93.5	63~ 66[a]
〃	4	〃	7	90.0	63~ 66
〃	3	THF	7	40.0	—
〃	4	〃		40.0	—

a) Produced as amorphous caramel which easily oxidized on recrystallization hence, it was converted into its picrate salt (see experimental part).

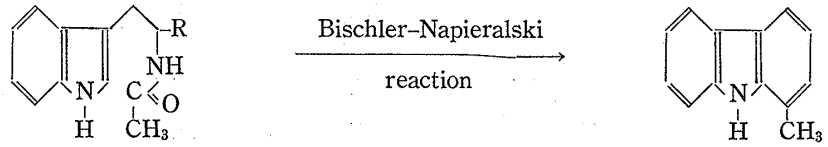
The products of these reactions were practically pure as indicated from their ultraviolet spectra where the characteristic indole peak of the starting thioamides was always absent and the 3,4-dihydro-9*H*-pyrido[3,4-*b*]indole peaks were clearly exhibited. In addition, in case of IVa and IVb, recrystallization of the crude products was easily accomplished from the proper solvent and their structure was established by analysis, infrared and ultraviolet spectra as well as by melting point of the pure bases and their picrates which were in agreement with the reported ones.[3~5] In case of IVc, recrystallization of the crude product was impossible due to partial oxidation

2) S. Yamada, A.-Mohsen M. E. Omar, T. Hino: This Belletin, **12**, 244 (1964) and references cited there.
3) I. D. Spenser: Can. J. Chem., **37**, 1851 (1959).
4) E. Späth, E. Ledrer: Ber., **63B**, 120 (1930).
5) Y. Asahina, S. Osada: Chem. Zentr., I, 1479 (1927).

of the methylene group of the benzyl residue which is known to undergo such property.[6] Consequently, the crude (Ⅳc) was converted to the corresponding picrate, purified by recrystallization and then its structure was determined by analysis. No isolation of any of the intermediate organic mercurials, as described in the previous paper,[1] was undertaken.

On the other hand, when the same conditions were applied in tetrahydrofuran, in which both reactants are freely soluble, the reaction seemed to be highly retarded and no hydrogen chloride gas was detected. The separation of cyclized products as mentioned above, gave Ⅳa~c in remarkably poor yield (Table Ⅱ). In addition, the crude products from these reactions were relatively impure when compared with those obtained from acetonitrile mixtures. The reason for such nature of reaction in tetrahydrofuran is not understandable at the present stage.

As regard to the cyclodesulfurization of N-(methylthiocarbonyl)tryptophan methyl ester (Ⅲ), a great deal of worth has been laid on the realization of such reaction because the Bischler-Napieralski reaction conditions were proved to be either completely unsuccessful in the cyclization of N-acetyltryptophan (Ⅵa) or its methyl ester (Ⅵb) as reported by Harvey, *et al.*[7] and Snyder and his co-workers,[8,9] they got harman (Ⅶ) as the sole product instead of 1-methyl-3,4-dihydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylic acid (Vb) or its methyl ester (Va) due to decarboxylation and aromatization of the cyclized ring as demonstrated in Chart 2, or led to a relatively poor yield of Vb as stated by Tschesche,*et al.*,[10] who cyclized Ⅵa with a mixture of phosphoryl bromide and polyphosphoric acid under moderate conditions. Moreover, although Spenser[3] could prepare Vb under the Pictet-Spingler reaction conditions, the reported yield was not encouraging to consider this method of significant synthetic value.



Ⅵa : R=COOH
Ⅵb : R=$COOCH_3$

Ⅶ

Chart 2.

In our case, the cyclodesulfurization of the thioamide (Ⅲ) was successfully effected when three moles of mercuric chloride were allowed to react with one mole of Ⅲ in acetonitrile under the previously established conditions and the cyclized products were obtained as a mixture of both 1-methyl-3,4-dihydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylic acid (Vb) and the corresponding methyl ester (Va) in an overall yield of 82%.

Thus, after treating the final reaction mixture in the usual manner to remove mercuric chloride from the cyclized bases followed by isolation of the unreacted thioamide or the formed acid amide, the aqueous layer was made distinctly alkaline with dil. ammonia and the resulted pinkish emulsion was rapidly extracted with ether. Evaporation of ether afforded Va as frothy pink residue which was difficult to recrystallize hence, it was converted to its picrate and identified by elemental analysis. The evaporation of the alkaline layer followed by its dissolution in the minimum amount of water and chromatography on Amberlite IR 120 (in H^+ form) gave, after elution with 7% ammonium hydroxide and evaporation of the eluates, the cyclized Vb

6) P. J. Julian, W. J. Karpel, A. Magnami, E. W. Meyer : J. Am. Chem. Soc., **70**, 180 (1948).
7) D. G. Harvey, E. J. Miller, W. Robson : J. Chem. Soc., **1941**, 153.
8) H. R. Snyder, C. H. Hansch, L. Katz, S. M. Parmerter : J. Am. Chem. Soc., **72**, 219 (1950).
9) H. R. Snyder, F. X. Werber : *Ibid.*, **72**, 2962 (1950).
10) R. Tschesche, H. Jensen, P. R. Rangachari : Ber., **37**, 1851 (1959).

as amorphous yellow powder. Recrystallization of this product from aqueous ethanol afforded the analytically pure sample of Vb identified by analysis and ultraviolet spectra which were similar to the reported one of the same compound.[3]

In other experiments, the use of four moles of mercuric chloride for each mole of III in acetonitrile, afforded the cyclized bases in almost the same yield as with three moles of mercuric chloride but the proportion of cyclized ester (Va) in the final product was slightly higher than that produced from the previous experiment.

Finally, the several attempts to effect the cyclodesulfurization of the thioamide (III) under milder conditions by performing the reaction in ether or at higher temperature by using dimethylcellosolve, led to poor yield and contaminated products. These evidences as well as the poor results which accompanied the utilization of tetrahydrofuran, are good proof that acetonitrile is the most favorable solvent for this cyclodesulfurization reaction.

The successful application of this cyclodesulfurization reaction in synthesizing these 1,3-disubstituted-3,4-dihydro-9*H*-pyrido[3,4-*b*]indole derivatives has opened a wide scope for extending its utilization to the cases in which the classical Bischler-Napieralski reaction either fails completely or produces poor results.

Experimental*4

Tryptamine (I: R=H) was synthesized from indole according to the reported methods by being first converted to gramine[11] then led to its trimethyl ammonium methyl sulfate salt,[12] indole-3-acetonitrile[12] and finally reduced with Raney Ni[13] to give the crude product which on being recrystallized from benzene afforded tryptamine as yellowish prisms, m.p. 115~116°(reported,[13] m.p. 116~117°).

General Procedure for the Preparation of N-[2-(3-Indolyl)ethyl]thioamides (IIa~c)——A solution of tryptamine in the minimum amount of MeOH was treated with the equivalent amount of the required ethyl dithioester, prepared as reported in case of N-(2-arylethyl)thioamides,[1] and the mixture was cooled in ice for 1 hr., when soon a vigorous smell of mercaptan was detected. The solvent was then evaporated under reduced pressure on a steam bath and the residue was heated in boiling water bath within a period of 15~30 min., then heated *in vacuo* for the same period to remove traces of mercaptan. The product which always solidified after cooling *in vacuo*, was recrystallized from the proper solvent as recorded in Table I.

Tryptophan Methyl Ester Hydrochloride——This was prepared from tryptophan according to the reported method from our laboratory for the esterification of 1-alkyltryptophan.[14] The crude product after being washed successively with MeOH, MeOH-ether (1:1), ether and dried, was obtained as chalky white powder, m.p. 236°(decomp.), which was used in the preparation of the thioamide (III) without further purification. Yield 82%.

N-(Methylthiocarbonyl)tryptophan Methyl Ester (III)——Tryptophan methyl ester was converted to the free methyl ester according to the reported method,[13] the calculated amount of the resulted yellow viscous oil was dissolved in the minimum amount of MeOH and treated with the equivallent amount of ethyl dithioacetate and the mixture was subjected to the same treatment as in the general procedure. Results are listed in Table I.

General Procedure for the Cyclodesulfurization of N-[2-(3-Indolyl)ethyl]thioamides (IIa~c) with Mercuric Chloride——A solution of one mole of the thioamides (IIa~c) in the chosen solvent was mixed with the solution of either 3 or 4 moles of $HgCl_2$ in the same solvent as shown in Table II and the mixture was stirred under reflux for 7 hr., when the initial clear yellow reaction mixture changed to white turbid, yellowish brown with evolution of HCl gas (in case of using CH_3CN only) and finally to brown with white creamy amorphous powder suspended in it. This was diluted with excess solvent, acidified with few drops of 10% aq. HCl and saturated with H_2S. The resulted HgS was filtered and the filtrate was evaporated to leave yellowish brown residue which was dissolved in warm H_2O, cooled and extracted repeatedly with ether. The ether layer was washed well with H_2O, dried over anhyd. Na_2SO_4, filtered and the solvent removed to afford either the unreacted part of the starting thioamides or the produced acid amides identified by IR in

*4 All melting points are not corrected.

11) J. P. Greenstein, M. Winitz: "Chemistry of the Amino Acids," Vol. III, 2331 (1961), John Wiley and Sons, Inc. New York. London.
12) C. Schöpf, J. Thesing: Angew. Chem., **63**, 377 (1951).
13) J. Thesing, F. Schüle: Ber., **85**, 324 (1952).
14) S. Yamada, T. Shioiri, T. Itaya, T. Hara, R. Matsueda: This Bulletin, **13**, 88 (1965).

$CHCl_3$ and TLC. The aqueous layer was made distinctly alkaline with 10% aq. NaOH in case of IIa and IIb and with saturd. aq. $NaCO_3$ in case of IIc to give yellowish white emulsion which was thoroughly extracted with ether, the ether dried over anhyd. Na_2SO_4 and evaporated to yield the cyclized bases (IVa~c) in almost pure state as indicated from their UV where the indole bands at 290 mμ of the starting thioamides (IIa~c) were absent.

1-Methyl-3,4-dihydro-9*H*-pyrido[3,4-*b*]indole (IVa)——Separated as frothy pinkish residue which on recrystallization by extraction in a Soxhlet apparatus with either ligroin or petr. ether, was obtained as fluffy needles, m.p. 178~180°(Spenser,[3] reported m.p. 178~179° and Späth, *et al.*[4] reported m.p. 182°). *Anal.* Calcd. for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.21. Found: C, 78.36; H, 6.83; N, 15.17. UV λ_{max}^{EtOH} mμ (log ε): 234 (4.19), 240 (4.18), 315 (4.18). $\lambda_{max}^{EtOH+H^+}$ mμ (log ε): 245 (4.02), 349 (4.35). Picrate from EtOH, yellow needles charred at 221° and melted at 239°(decomp.). Recrystallization from 90% EtOH gave yellow needles, m.p. 245~246°(decomp.). *Anal.* Calcd. for $C_{18}H_{15}O_7N_5$: C, 52.3; H, 3.88; N, 17.26. Found: C, 52.28; H, 3.74; N, 16.94.

1-Phenyl-3,4-dihydro-9*H*-pyrido[3,4-*b*]indole (IVb)——Obtained as yellow prisms, m.p. 217~218°, which on being recrystallized from 90% MeOH afforded the analytically pure sample, m.p. 218.5~220°. *Anal.* Calcd. for $C_{17}H_{14}N_2$: C, 82.90; H, 5.73; N, 11.37. Found: C, 83.03; H, 5.86, N, 11.36. UV λ_{max}^{EtOH} mμ (log ε): 231 (4.33), 247 (4.38), 323 (4.12). $\lambda_{max}^{EtOH+H^+}$ mμ (log ε): 253 (4.04), 276 (3.94), 287 (3.92), 368 (4.34). Picrate from aq. EtOH, yellow prisms, m.p. 243~245°, which on recrystallization from acetone was obtained as yellow prisms, m.p. 246~247°(decomp.). *Anal.* Calcd. for $C_{23}H_{17}O_7N_5$: C, 58.10; H, 3.60; N, 14.73. Found: C, 57.73; H, 3.51; N, 14.78.

1-Benzyl-3,4-dihydro-9*H*-pyrido[3,4-*b*]indole (IVc)——Produced as yellow frothy residue which showed the normal absorption bands of the cyclized product in IR at 1616, 1598, 1574 (vw) and 1548 cm^{-1}. On attempted recrystallization from either benzene–hexane mixture or ether, it developed a band at 1664 cm^{-1} (m). Therefore, in other experiments, the product was directly converted into its picrate in MeOH to give tan crystals which on recrystallization from 95% EtOH afforded transparent yellow prisms, m.p. 225~226° (decomp.). *Anal.* Calcd. for $C_{24}H_{19}O_7N_5$: C, 58.89; H, 3.91; N, 14.31. Found: C, 58.59; H, 3.79; N, 14.15.

Cyclodesulfurization of N-(Methylthiocarbonyl)tryptophan Methyl Ester (III) with Three Moles of Mercuric Chloride——A solution of 1 g. (3.62 mmoles) of III in 25 ml. of anhyd. CH_3CN was mixed with a solution of 3 g. (10.86 mmoles) of $HgCl_2$ in 25 ml. of the same solvent and the mixture was stirred under reflux for 7 hr., when the initial clear mixture gradually changed to white turbid, yellow turbid near reflux, slightly tan with evolution of HCl gas and finally to brown with creamy amorphous powder. The resulted mixture was diluted with additional 40 ml. of CH_3CN, acidified with few drops of 10% aq. HCl and saturated with H_2S till no more black HgS was formed. HgS was filtered and the filtrate was evaporated to leave brown frothy residue which was taken in 200 ml. of warm H_2O, cooled and extracted repeatedly with ether. The ether was washed well with H_2O, dried over anhyd. Na_2SO_4, filtered and the solvent evaporated to afford a minute amount of the corresponding acid amide (VIb) identified by IR in $CHCl_3$ and TLC. The aqueous layer was made distinctly alkaline with dil. aq. NH_4OH and the produced pinkish emulsion was rapidly extracted with ether. This ether was washed well with H_2O, dried over anhyd. Na_2SO_4 and evaporated under reduced pressure to give 300 mg. of frothy pink residue whose UV showed no peaks of the indole residue and exhibited a bathochromic shift on addition of acids. The attempted recrystallization of this product from benzene–hexane mixture was unsuccessful. Therefore, it was converted into its picrate in 95% EtOH to afford orange yellow prisms, m.p. 245~246°, which on being recrystallized from 80% EtOH yielded the analytically pure sample of methyl 1-methyl-3,4-dihydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (Va) picrate as orange yellow prisms, m.p. 246.5~247°(decomp.). *Anal.* Calcd. for $C_{20}H_{17}O_9N_5$: C, 50.96; H, 3.64; N, 14.86. Found: C, 50.82; H, 3.99; N, 14.6.

The aqueous alkaline layer was evaporated to dryness and the residue dissolved in 50 ml. of H_2O and then chromatographed on 50 ml. of Amberlite IR 120 (H^+), after the column was washed well with dist. H_2O till neutral, and eluted with 7% aq. NH_4OH. The eluates were evaporated to leave 400 mg. of yellow amorphous powder, m.p. 197~199°(decomp.), which on being recrystallized from 80% EtOH, afforded the analytically pure 1-methyl-3,4-dihydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylic acid (Vb) as yellow amorphous powder, m.p. 199.5~200°(decomp.). *Anal.* Calcd. for $C_{13}H_{12}O_2N_2 \cdot \frac{1}{2}H_2O$: C, 65.81; H, 5.52; N, 11.81. Found: C, 66.18; H, 5.43; N, 12.16. IR ν_{max}^{Nujol} cm^{-1}: 1655 (m), 1615 (m), 1592 (s), 1570 (s), 1523 (m). UV λ_{max}^{EtOH} mμ (log ε): 237 (4.02), 350 (4.22). $\lambda_{max}^{EtOH+OH^+}$ mμ (log ε): 237 (4.3), 315 (4.16). $\lambda_{max}^{EtOH+H^+}$ mμ (log ε): 240 (3.96), 353 (2.29). Overall yield was 82%.

Cyclodesulfurization of N-(Methylthiocarbonyl)tryptophan Methyl Ester (III) with Four Moles of Mercuric Chloride——This experiments was performed by stirring a mixture of 1 g. of III and 4 g. of $HgCl_2$ in 50 ml. of anhyd. CH_3CN under the above conditions. The separation of the products was effected as described in the previous procedure to yield 400 mg. (45.6%) of Va and 300 mg. (36.3%) of Vb. The products were identified as mentioned in the above experiment. Overall yield was 81.9%.

The authors wish to thank the members of the Central Analysis Room of this faculty for microanalytical data and the measurement of the infrared and ultraviolet spectra.

Summary

Three new N-[2-(3-indolyl)ethyl]thioamides (IIa~c) and N-(methylthiocarbonyl) tryptophan methyl ester (III) were conveniently prepared according to our general procedure of synthesizing thioamides. The cyclodesulfurization of IIa~c was successfully accomplished in high yield to the corresponding 1-substituted-3,4-dihydro-9*H*-pyrido[3,4-*b*]-indole derivatives (IVa~c). In addition, III was cyclized to give a mixture of both 1-methyl-3,4-dihydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylic acid (Vb) and its methyl ester (Va) in excellent yield.

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115. Eizo Hirai : The Behavior of 4-Amino-5-carboxy-2-methylpyrimidine in Aqueous Solution.

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In the previous paper[1] it was found that the base strength of 4-amino-5-carboxy--2-methylpyrimidine (ACMP) was much lower than that estimated from the Hammett equation for the basic pKa value of 4,5-substituted 2-methylpyrimidines. Such deviation may result from any one of the following causes : (a) amino-imino tautomerism; (b) interaction between the carboxyl group and the neighboring amino group in the molecule; and (c) interaction between the carboxy group and the nuclear nitrogen atom in the molecule. However, it is impossible to attribute the deviation of ACMP from the Hammett equation to (a), because a similar deviation was found on the 4-dimethylamino analogue of ACMP, which necessarily possesses the amino structure. If it is caused by (b), considerable depression of base strength may be found on 2-aminonicotinic acid (ANA), but not so on 2-aminoisonicotinic acid (AINA). If it is caused by (c), depression may be found on both the base strengths of ANA and AINA. Hence the author examined the Hammett equations for the base strength of both series of 3- and 4-substituted 2-aminopyridines containing ANA and AINA prior to discussion of the behavior of ACMP in the present study.

Results and Discussion

The basic ionization constants of 3- and 4-substituted 2-aminopyridines are potentiometrically and spectrophotometrically determined. Since ANA and AINA are amphoteric, the acidic ionization constants also are spectrophotometrically determined. These constants are listed in Table I. As shown in Fig. 1, each Hammett equation for the basic pKa values of both series of 2-aminopyridines is represented by a linear relationship, with the exception of ANA and AINA. The meta- and para-substituent constants, σ_m and σ_p, are used as a measure of polar effect of the 3- and

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1) S. Mizukami, E. Hirai : J. Org. Chem., **31**, 1199 (1966).